

APPENDIX B
Version with Markings to Show Changes Made
37 C.F.R. § 1.121(b)(iii) and (c)(ii)

SPECIFICATION:

Paragraph at page 3, lines 11-15:

The present invention also provides a liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 10 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween] TWEEN[®] 80.

Paragraph at page 3, lines 16-20:

The present invention further provides a liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween] TWEEN[®] 80.

Paragraph at page 12, line 24 to page 13, line 15:

Example 1

The following study examines the effect of the concentration of citric acid on the bioavailability and plasma concentration of nasally administered salmon calcitonin. Rats were administered intranasally as described previously 20 μ l of rsCT (200 μ g/ml) in 0.85% sodium chloride, 0.1% [Tween] TWEEN[®] 80, 0.2% phenylethyl alcohol, 0.5% benzyl alcohol and varying amounts of citric acid adjusted to pH 3.7 at t=0, 20, 60 and 90 minutes. Samples of blood were taken prior to the administration of rsCT at these time points as well as at t=120 and 150 minutes. The resulting plasma samples were analyzed for rsCT by radioimmunoassay. Maximum rsCT levels were detected at t=120 minutes. The results of this study as shown in Table 1 indicate that the bioavailability and peak concentration of rsCT was a function of the concentration of citric acid in the formulation.

Paragraph at page 14, lines 12-24:

Example 2

The following study examines the effect of different preservatives on the plasma concentration of nasally administered salmon calcitonin. Rats were administered intranasally as

described previously 20 μ l of sCT (200 μ g/ml) in 0.85% sodium chloride, 0.1% [Tween] TWEEN[®] 80 and a combination preservatives of either 0.2% phenylethyl alcohol and 0.5% benzyl alcohol or 0.27% methyl parabens and 0.04% propyl parabens at t=0, 30, 60 and 90 minutes. The results of this study as shown in Table 2 indicate that the bioavailability and peak concentration of rsCT are not significantly affected by the addition of the different preservatives.

Paragraph at page 15, line 11 to page 16, line 6:

Example 3

The following study examines the effect of the concentration of citric acid on the stability of salmon calcitonin stored for varying periods at a temperature of 50°C. Nasal formulations containing sCT (200 μ g/ml), 0.25% phenylethyl alcohol, 0.5% benzyl alcohol and 0.1% [Tween] TWEEN[®] 80 were adjusted to pH 3.7 with either HCl or the indicated amount of buffered citric acid. The formulations were stored at 50°C in sealed glass containers for the indicated amount of time and analyzed for sCT by high performance liquid chromatography. The results as shown in Table 3 indicate that in the absence of citric acid, the amount sCT in the formulation decreased steadily between 0 and 9 days after the study was begun. In the presence of citric acid (10-50 mM) the rate of disappearance of sCT decreased significantly. However, as the concentration of citric acid was further increased, the rate of sCT disappearance from vials stored at 50°C increased in proportion to the amount of buffered citric acid in the formulation.

CLAIMS:

16. The liquid pharmaceutical composition of claim 1 further containing at least 0.1% by weight of [Tween 80] polyoxyethylene(20) sorbitan monooleate.

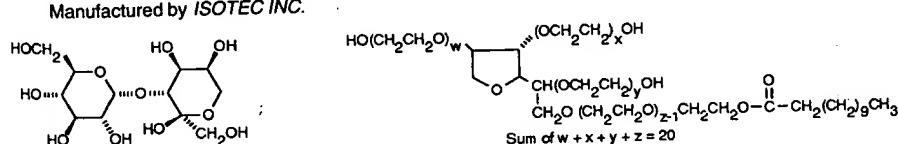
18. A liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 10 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween 80] polyoxyethylene(20) sorbitan monooleate.

19. A liquid pharmaceutical composition comprising about 2,200 MIC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween 80] polyoxyethylene(20) sorbitan monooleate.



■ Tungsten s ■

+% [7440-33-7] W FW 183.85	10g	38.10	39,944-2	Tungsten silicide, -325 mesh [12039-88-2] WSi ₂ FW 240.02	10g	16.1
TECS# Y07175000 FLAMMABLE SOLID	100g	249.80	24,363-9	Tungsten(IV) sulfide, powder, <2 micron, 99% [12138-09-9] WS ₂ FW 247.98	50g	32.1
i% [7440-33-7] W	10g	21.10	★	d 7.500 Safety 2,3559B R&S 1(3),3299E IRRITANT	50g	30.1
5-1.0 micron, 99.9+% [7440-33-7] W	50g	69.80	Tungsten tetrachloride, see 26,397-4, Tungsten(IV) chloride page 1712			
99.9+%, in hexanes [7440-33-7] W	100g	14.30	45,906-2	Tungstic acid, 99.999% [7783-03-1] H ₂ WO ₄ FW 249.86 d 5.500	5g	33.1
Merck Index 12,9948 FT-IR 1(2),1246C RTECS# Y07840000 IRRITANT	500g	47.80	★	Merck Index 12,9948 FT-IR 1(2),1246C RTECS# Y07840000 IRRITANT	25g	109.1
99.9+%, in hexanes [7440-33-7] W	5g	25.30	22,332-8	Tungstic acid, 99% [7783-03-1] H ₂ WO ₄	5g	16.1
Merck Index 12,9945 FLAMMABLE LIQUID			★		100g	29.1
~100 nm diameter powder which may structure and internal energy					500g	114.1
[7440-33-7] W						
~100 nm diameter powder which may structure and internal energy	100g	26.60	Tuppy's maleimide, see D14,080-5, N-(4-Dimethylamino-3,5-dinitrophenyl)maleimide page 637			
[7440-33-7] W FW 183.85	500g	94.50	28,737-7	o-Turanose, 98% [547-25-1] (3-O- α -D-glucopyranosyl-D-fructose) FW 342.30	1g	24.1
S 1(3),3227J RTECS# Y07175000	24g	63.15	mp 170°(dec) [α] _D +75°(c=4, H ₂ O) Beil. 31,454 Merck Index 12,9951	5g	99.1	
FT-NMR 1(1),308C R&S 1(1),197F			Turquoise Blue, see 30,647-9, Reactive Blue 15 page 1460			
[7440-33-7] W	15g	34.10	27,434-8	Tween® 20 [9005-64-5] [polyoxyethylene(20) sorbitan monolaurate] n _D 1.4680	25mL	11.1
[7440-33-7] W	18.9g	46.00	★	d 1.095 Fp >230°F(110°C) R&S 1(1),761E RTECS# TR7400000	500mL	17.1
94.5g	170.90	Average M _n ca. 1,228. HLB 16.7	4L	57.1		
6 [7440-33-7] W	9.5g	28.40	27,435-6	Tween® 40 [9005-66-7] [polyoxyethylene(20) sorbitan monopalmitate] n _D 1.4700	25mL	12.1
95g	179.05	★	d 1.083 Fp >230°F(110°C) R&S 1(1),761F RTECS# WG2933000	500mL	17.1	
Average M _n ca. 1,284. HLB 15.6	4L	58.1				
1 solution d 1.010 Fp none Safety 2,3558A...	100mL	16.60	37,425-3	Tween® 60 [9005-67-8] [polyoxyethylene(20) sorbitan monostearate] d 1.044...	25mL	11.1
Exact W concentration on label			★	Fp >230°F(110°C) R&S 1(1),761G RTECS# WG2934000	500mL	17.1
1 solution d 1.010 Fp none Safety 2,3558B...	100mL	16.60	Average M _n ca. 1,312. HLB 14.9	4L	59.1	
Exact W concentration on label			27,436-4	Tween® 80 [9005-65-6] [polyoxyethylene(20) sorbitan monooleate] n _D 1.4720	25mL	1.1
d 1.012 Fp none			★	d 1.064 Fp >230°F(110°C) Merck Index 12,7742 R&S 1(1),761H RTECS# WG2932500	500mL	1.1
W concentration on label	100mL	45.70	IRRITANT	4L	5.1	
9-10			Average M _n ca. 1,310. HLB 15.0	18L	19.1	
007-09-9] WB FW 194.66 R&S 1(3),3265H ..	25g	28.20	38,890-4	Tween® 85 [9005-70-3] [polyoxyethylene(20) sorbitan trioleate] n _D 1.4680	25mL	1.1
r ₅ FW 583.40 CORROSIVE	1g	14.70	★	d 1.028 Fp >230°F(110°C) R&S 1(1),761I RTECS# WG2934500	500mL	1.1
5g	48.30	Average M _n ca. 1,839. HLB 11.0	4L	5.1		
99% [12070-12-1] WC FW 195.86	100g	29.70	21,679-8	Twort Stain λ_{max} 634(539)nm FT-IR 1(2),1043C Safety 2,3561B R&S 1(2),2843F	10g	3.1
Y07250000	500g	116.30	UV-Vis 723 CANCER SUSPECT AGENT			
8] (tungsten tetrachloride) WCl ₄	5g	47.50	A 1 to 1 complex of Light Green SF and Neutral Red used as a stain for microorganisms			
D CORROSIVE MOISTURE-SENSITIVE	25g	158.00	in tissues and in the staining of bacteria, yeasts and algae under various conditions.			
01-7] WCl ₆ FW 396.57 mp 275° bp 347°	10g	48.70	21,679-8	Twort Stain λ_{max} 634(539)nm FT-IR 1(2),1043C Safety 2,3561B R&S 1(2),2843F	10g	3.1
R&S 1(3),3335E RTECS# Y07710000	100g	208.10	UV-Vis 723 CANCER SUSPECT AGENT			
6	100g	71.40	A 1 to 1 complex of Light Green SF and Neutral Red used as a stain for microorganisms			
6x100g	318.10	in tissues and in the staining of bacteria, yeasts and algae under various conditions.				
13520-76-8] WO ₂ Cl ₂ FW 286.76	1g	17.20	T9,034-4	Tyramine, 99% [51-67-2] [4-(2-aminoethyl)phenol] HO ₂ C ₆ H ₄ CH ₂ CH ₂ NH ₂	5g	1.1
10g	95.00	FW 137.18 mp 161-163° bp 175-181°/8mm Beil. 13,625 Merck Index 12,9966	25g	1.1		
-6] (tungsten hexafluoride) WF ₆	225g†	298.60	FT-NMR 1(2),612A FT-IR 1(1),1289C Safety 2,3562A R&S 1(1),1489I			
12,9946 RTECS# Y07720000	450g†	453.70	RTECS# SJ5950000 IRRITANT			
+% [14040-11-0] W(CO) ₆ FW 351.91	5g	85.20	T9,035-2	Tyramine hydrochloride, 98% [60-19-5] [4-(2-aminoethyl)phenol hydrochloride]	5g	1.1
	25g	284.00	HO ₂ C ₆ H ₄ CH ₂ CH ₂ NH ₂ ·HCl FW 173.65 mp 271-274° Beil. 13,625 Merck Index 12,9966	25g	1.1	
-0] W(CO) ₆	10g	36.40	FT-NMR 1(2),612B FT-IR 1(1),1289D Safety 2,3562B R&S 1(1),1489J			
	50g	130.00	RTECS# SJ6050000 IRRITANT			
22-5] WO ₂ FW 215.85 IRRITANT	10g	25.50	T9,039-5	DL-m-Tyrosine, 99% [775-06-4] [3-(3-hydroxyphenyl)-DL-alanine]	1g	1.1
	50g	81.60	HO ₂ C ₆ H ₄ CH ₂ CH(NH ₂)CO ₂ H FW 181.19 mp 280-285°(dec.) Beil. 14,605	5g	1.1	
1] WO ₃ FW 231.85 d 7.160	10g	48.00	FT-NMR 1(2),1187A FT-IR 1(2),254D R&S 1(2),1845I RTECS# YP2278000 IRRITANT			
(3),3283K RTECS# Y07760000 IRRITANT	50g	149.30	85,545-6	DL-Tyrosine, 99% [556-02-5] [(R)-(+)-tyrosine, 3-(4-hydroxyphenyl)-DL-alanine]	500mg	1.1
	250g	578.20	★	4-(HO)C ₆ H ₄ CH ₂ CH(NH ₂)CO ₂ H FW 181.19 mp >300° [α] _D +10.3° (c=4, 1N HCl)	1g	1.1
, 99+% [1314-35-8] WO ₃	100g	32.10	Beil. 14,605 FT-NMR 1(2),1188A FT-IR 1(2),255C Safety 2,3565A R&S 1(2),1845M	5g	1.1	
	500g	105.60	IRRITANT			
	2kg	288.30	48,890-9	DL-Tyrosine- β - ¹³ C, 98 atom % ¹³ C [93627-94-2] 4-(HO)C ₆ H ₄ ¹³ CH ₂ CH(NH ₂)CO ₂ H	250mg	4.1
	5g	59.50	FW 182.19 mp 325°(dec.) IRRITANT			
	25g	205.30	Manufactured by ISOTEC INC.			
'8-0] WOCl ₄ FW 341.66 mp 211°			49,232-9	DL-Tyrosine- ¹⁵ N, 99 atom % ¹⁵ N [35693-13-1] 4-(HO)C ₆ H ₄ CH ₂ CH(¹⁵ NH ₂)CO ₂ H	500mg	2.1
SENSITIVE IRRITANT			FW 182.19 mp 235°(dec.) IRRITANT			
			Manufactured by ISOTEC INC.			



28,737-7

27,434-8